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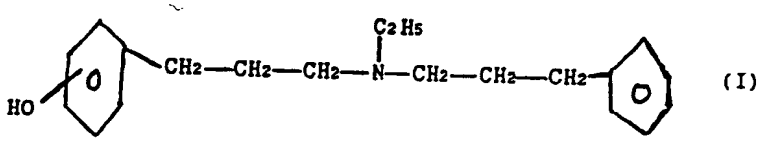
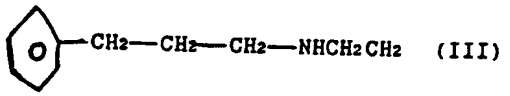
(54) Title: PROPYLAMINE DERIVATIVES



(I)



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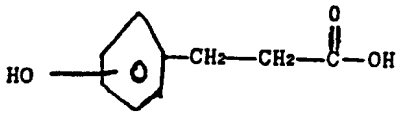

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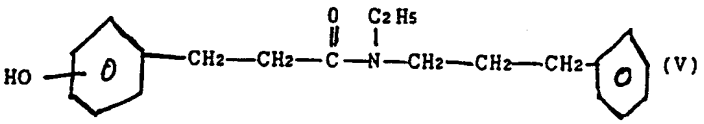

(V)

(57) Abstract

Novel propylamine derivatives having general formula (I) and quaternary bases thereof. Such compounds exhibit antispasmodic activity. Compounds (I) may be prepared by coupling a compound having formula (III) with a compound having general formula (IV) to produce a compound having general formula (V) and reducing the compound (V) to the amine having general formula (I). The coupling agent may be dicyclohexyl carbodimide and the reducing agent may be lithium aluminium hydride.

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+ DESIGNATIONS OF "SU"

It is not yet known for which States of the former Soviet Union any designation of the Soviet Union has effect.

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TITLE

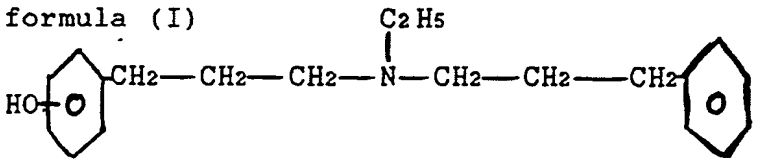
Propylamine Derivatives

Certain nitrogen containing materials, sometimes in the form of amines or quaternary bases, are known to possess antispasmodic activity.

The present invention provides a propylamine derivative (I) (hereinafter defined) which we have shown to possess significant antispasmodic properties.

The compound (I) is probably best used in one of its salt forms, e.g. its hydrochloride, as this increases water solubility and may improve its bioavailability.

According to one aspect of the invention there is provided a propylamine derivative having the general formula (I)



(I) or a quaternary base thereof.

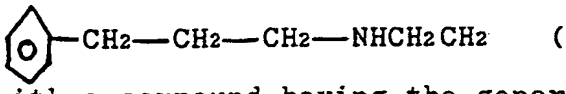
An especially useful compound within the general formula (I) is compound (II) which is N-ethyl, N-(3-phenyl propyl), 3-(4-hydroxyphenyl)-propylamine, i.e. the para hydroxy compound.

The said propylamine derivative (I) or (II) may be in the form of a pharmaceutically acceptable inorganic salt, e.g. the hydrochloride thereof, or organic salt, e.g. the citrate.

According to another aspect of the invention there is provided the use of the compound (I) or a quaternary base thereof, or a pharmaceutically acceptable salt thereof as an antispasmodic agent.

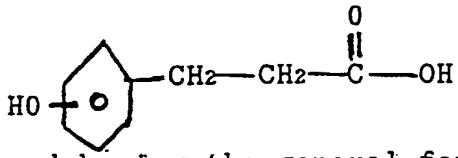
According to a further aspect of the invention there is provided a composition comprising a compound (I) or a quaternary base thereof or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor. Such a composition may be in the form of tablets, capsules, microspheres, liquid, semisolid or suppository dosage. Such a composition may be administered by oral, intravenous, intramuscular, topical or rectal route.

According to a still further aspect of the invention there is provided a method for the production of compound (I) comprising coupling, using a coupling agent, a compound having the formula (III)

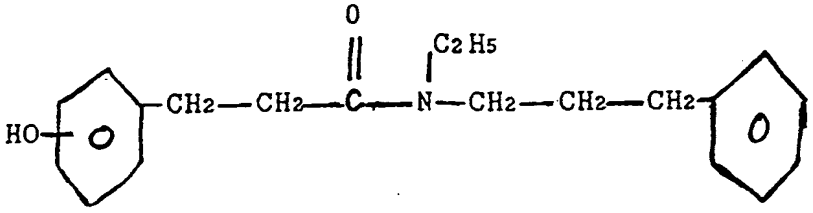


(III)

with a compound having the general formula (IV)



(1V) to produce a compound having the general formula (V)



(V)

and reducing, using a reducing agent, the compound (V) to the amine having the general formula (I) as defined above.

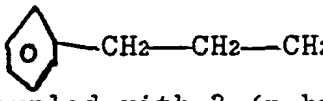
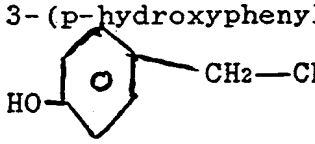
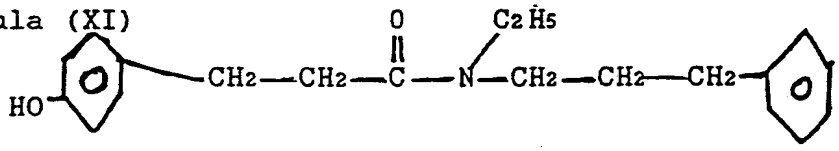
Preferably the said coupling agent is dicyclohexyl carbodimide, preferably in methylene chloride, and preferably the said reduction is achieved by the use of lithium aluminium hydride as reducing agent, preferably in diethyl ether.

Preparative Example

Preparation of N-ethyl, N-(3-phenyl propyl), 3-(4-hydroxyphenyl)-propylamine (II)

The synthesis commences with 3-(phenyl) propionic acid (dihydrocinnamic acid) (a) having the formula  (VI) which is converted to the corresponding acid chloride having the formula  (VII) with thionyl chloride (b). Treatment of this acid chloride (VII) with a large excess of anhydrous ethylamine gives a white crystalline amide having the formula (VIII)  in good yield. Reduction of the said amide with lithium aluminium hydride worked well in diethyl ether (c) (but not tetrahydrofuran) to give a thick yellow brown oil which was slower on TLC (thin layer chromatography). The distinctive pair of H^2 protons were observed at 1.8 ppm in the proton nuclear magnetic (^1H NMR) spectrum. The

product could be extracted into aqueous acid and gave a positive colour test with benzyl p-nitrophenyl formate due to the liberation of p-nitrophenol (yellow). Both of these are positive tests for the presence of an amine group.

The resultant amine which has the formula  (IX) was successfully coupled with 3-(p-hydroxyphenyl) propionic acid having the formula  (X) using dicyclohexyl carbodimide (DCC) in methylene chloride. The major part of the by-product, dicyclohexyl urea (DCU), was removed by filtration of the crude reaction mixture and the rest precipitated from a concentrated solution after aqueous work-up. The tertiary amide having the formula (XI)  gave the characteristic AB splitting pattern of the p-hydroxyalkyl moiety in the aromatic region of the ^{1}H NMR spectrum.

The amide (XI) was reduced using lithium aluminium hydride in diethyl ether, where the ether to amide ratio was in the range 20:1 to 30:1, (a b c) to give the required product N-ethyl, N-(3-phenyl propyl), 3-(4-hydroxyphenyl)-propylamine (II).

EXPERIMENTAL

N-ethyl 3-phenyl propylamide (VIII)

Prepared according to literature procedure. (b) ^1H NMR 7.6 (5H, s, aromatics); 3.2 (2H, m, $2H^2$); 2.9 (2H, m $2H^4$); 2.4 (2H, m, $2H^1$); 1.0 (3H, t, 7hz, $3H^5$).

N-ethyl 3-phenylproplylamine (IX)

Lithium aluminium hydride (5.78 g, 152 mmoles) was dissolved in dry diethyl ether (250 ml) in a 3 neck 1L flask fitted with a dropping funnel, reflux condenser, stopper and magnetic stirrer bar. All exits were closed with drying towers. The solution was brought to reflux and the heat removed. The amide (VIII) (16 g, 90 mmoles) dissolved in dry diethyl ether (250 ml) was added dropwise over 30 minutes with vigorous stirring. The solution was then refluxed for 36 hours. Water (700 ml) was added cautiously; the gummy gel was filtered and the filtrate extracted with ether (5 x 350 ml). The combined organic extracts were dried over magnesium sulphate, filtered and evaporated to give a yellow oil (14.5 g, 100%).

TLC Starting material Rf 0.46

Product Rf 0.2

Silica gel plates, eluant 98% chloroform, 2% methanol/^1H NMR ($CDC1_3$) 7.2 ppm (5H, m, aromatics); 2.65 (6H, m, $2H^1$, $2H^3$, $2H^4$); 1.8 (2H, m, $2H^2$); 1.1 (3H, t, 7hz, $3H^5$).

N-ethyl, N-(3-phenylpropyl), 3-(4-hydroxyphenyl)-propylamide (XI)

The acid (X) (50 g, 0.3 mole) and DCC (32 g, 0.16 mole) were suspended in methylene chloride (200 ml). The amine (IX) (16 g, 0.1 mole) was added dropwise from a pressure equalised dropping funnel. A mild exotherm was produced. After two hours stirring the reaction mixture was filtered and the filtrate poured into saturated sodium bicarbonate (300 ml) which was extracted with methylene chloride (5 x 200 ml). The collected extracts were dried with sodium sulphate and evaporated to give an orange oil (51.68 g). The precipitate which was filtered off was shown to consist entirely of DCU by ^1H NMR. The oil was dissolved in hot benzene, additional DCU precipitated and was filtered off (yield 30 g, 93%). ^1H NMR ($CDCl_3$) 7.5-6.9 ppm (10H, m, aromatics, OH); 3.5-2.2 (10H, m, $2H^1$, $2H^2$, $2H^4$, $2H^6$, $2H^7$); 2-1.5 (2H, m, $2H^5$); 1.1 (3H, t, 7hz, $3H^8$).

N-ethyl, N-(3-phenylpropyl), 3-(4-hydroxyphenyl)-propylamine (II).

Lithium aluminium hydride (20 g, 52 mmoles) was dissolved in dry diethyl ether (1L, CaH_2 dried) in a 10L three neck flask fitted with a reflux condenser, dropping funnel, stopper and a magnetic stirrer. All exits were closed with drying tubes. The amide (XI) 40 g, 12.8

mmoles) in dry diethyl ether (1L) was added dropwise to a gently refluxing solution, over 1 hour. The condenser was transferred to the dropping funnel and the funnel was washed clean by reflux. The condenser was then returned to its former position and reflux maintained for 4 hours. Addition of water (5 ml) and magnesium sulphate heptahydrate (100 g) gave a solid which which was filtered and washed with water (2L) and diethyl ether in alternate small portions. Separation of the phases and extraction of the aqueous phase with ether (8 x 300 ml) followed by magnesium sulphate drying, filtration and evaporation gave a yellow oil, which was further dried by azeotrope with benzene. The aqueous phases had a pH of 11 which is a little too high for a phenol extraction. Accordingly, hydrochloric acid was added to pH5 and this was neutralised with sodium bicarbonate to pH8. However, further extraction only gave traces of 3-(4-hydroxyphenyl) propionic acid (confirmed by ^1H NMR).

TLC Product Rf 0.2 eluant 95% chloroform, 5% methanol ^1H NMR ($CDC1_3$) 7.4 ppm (5H, m, phenyl); 7.2 (2H, 8hz, aromatics, part of AB pair); 6.2 (1H, brs, OH); 2.5 (10H, $2H^1$, $2H^3$, $2H^4$, $2H^6$, $2H^7$); 1.8 (4H, m, $2H^2$, $2H^5$); 1.0 (3H, t, 7hz, $3H^8$).

Antispasmodic Activity

Antispasmodic activity was determined using standard

methodology. (d)

Guinea-pig ileum muscle was suspended in a gut bath, in oxygenated Tyrode's solution at 37°. Doses of acetylcholine were added to the gut bath fluid, the contraction recorded, and the bath washed out with fresh Tyrode's solution. This was carried out repeatedly to establish a dose of acetylcholine to cause a sub-maximal response. This dose of acetylcholine was used repeatedly, on a 2 minute cycle to establish steady responses. Doses of antispasmodic were then added 30 seconds before the acetylcholine dose to establish the magnitude of reduction of the acetylcholine contraction.

Using atropine sulphate as a standard, N-ethyl, N-(3-phenyl propyl) 3-(4-hydroxyphenyl)-propylamine (II) in the hydrochloride form was shown to have an antispasmodic activity approximately 25 times less than the standard (1.5 ng of the said amine hydrochloride was equivalent to 0.06 ng of atropine sulphate.)

Literature references (a) - (d) are listed below.

References:

(a) T. Hudlicky, Reductions in Organic Chemistry, Ellis Horwood, Chichester, 1984.

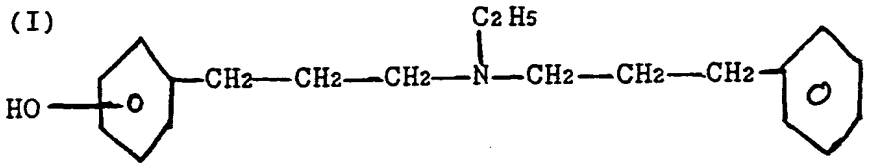
(b) A.C. Cope and E Ciganek, Organic Synthesis, 1960, 39, 19.

(c) V.M. Micovic and M.L. Mihailovic, J. Org. Chem., 1953, 18, 1190.

(d) Pharmacological Experiments on Isolated Preparations, E & S Livingstone Edinburgh and London, 1970.

CLAIMS

1. A propylamine derivative having the general formula (I)



(I)

or a quaternary base thereof.

2. N-ethyl, N- (3- phenyl propyl), 3- (4-hydroxyphenyl) - propylamine or a quaternary base thereof.

3. A compound as defined in Claim 1 or Claim 2 which is in the form of a pharmaceutically acceptable inorganic salt.

4. A compound according to Claim 3 which is in the form of a hydrochloride thereof.

5. A compound as defined in Claim 1 or Claim 2 which is in the form of a pharmaceutically acceptable organic salt.

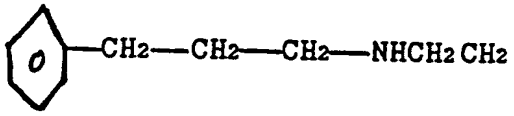
6. A compound according to Claim 5 which is in the form of a citrate thereof.

7. The use of a compound as defined in any one of Claims 1 to 6 as an antispasmodic agent.

8. A composition comprising a compound as defined in any one of Claims 1 to 6 and a pharmaceutically acceptable carrier therefor.

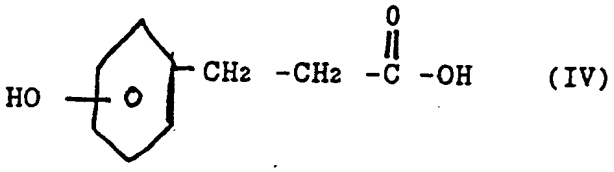
9. A composition according to Claim 8 which is in the form of tablets, capsules, microspheres, liquid, semisolid or suppository dosage.

10. A method for the production of a compound (I) comprising coupling, using a coupling agent, a compound having the formula (III)



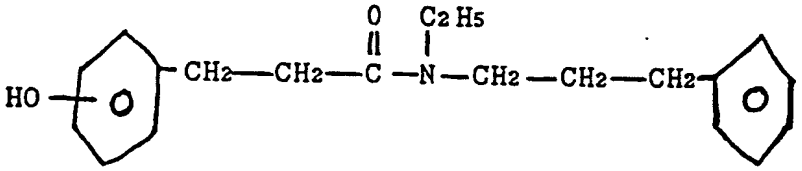
(III)

with a compound having the general formula (IV)



(IV)

to produce a compound having the general formula (V)



(V)

and reducing, using a reducing agent, the compound (V)

to the amine having the general formula (I).

11. Method according to Claim 10, wherein the said coupling agent is dicyclohexyl carbodimide.

12. Method according to Claim 10 or Claim 11, wherein said reduction is achieved by the use of lithium aluminium hydride as reducing agent.

13. A propylamine derivative as claimed in any one of Claims 1 to 6 for use as an active pharmaceutical substance.

14. A propylamine derivative as claimed in any one of Claims 1 to 6 for use as an antispasmodic agent.

15. A method according to Claim 10 substantially as herein described and exemplified.

16. A compound as defined in any one of Claims 1 to 6 substantially as herein described and exemplified.

17. A composition according to Claim 8 substantially as herein described and exemplified.

INTERNATIONAL SEARCH REPORT

International Application PCT/GB 91/01348

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C215/54; A61K31/135

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	CHEMICAL ABSTRACTS, vol. 78, no. 11, 19 March 1973, Columbus, Ohio, US; abstract no. 67072D, IRESON,J,D: 'Effects of Alverine citrate on smooth muscle' page 38 ;column 1 ; see abstract & PHARMACOLOGICAL RESEARCH COMMUNICATIONS vol. 4, no. 3, 1972, pages 191 - 194; & CHEMICAL SUBSTANCE INDEX,PAGE 5419CS 'Benzenepropanamine,N-ethyl-N-(3-phenylpropyl)-' ---	1-17

° Special categories of cited documents :[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08 NOVEMBER 1991	02.12.91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	i.m.helps I.M. Helps.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101348 SA 50358

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
/*- -		FR-A- 1515687 GB-A- 115410 NL-C- 133871 NL-A- 660376	

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